Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 06/06/2024

Enhertu® (fam-trastuzumab deruxtecan-nxki)

HCPCS: J9358

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Prescribed by or in consultation with an oncologist
   b. FDA approved age
   c. Unresectable or metastatic HER2-positive breast cancer
      i. Must have had disease progression or toxicity while on at least one prior trastuzumab-based regimen given for unresectable/metastatic disease
      OR
      ii. For use as first-line therapy in situations where there has been rapid progression during or within 6 months following adjuvant or neoadjuvant therapy that did not contain pertuzumab OR within 12 months for those on a pertuzumab-containing regimen
      iii. Human epidermal growth factor receptor 2 (HER2) positive is defined as follows:
         1. Immunohistochemistry (IHC) is 3+
         OR
         2. In situ hybridization (ISH) positive by any of the following:
            a) Single probe average HER2 copy number greater than or equal to 6.0 signals/cell
            OR
            b) Dual probe HER2/CEP17 ratio greater than or equal to 2.0
            OR
            c) Dual probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell
   d. Unresectable or metastatic HER2-low breast cancer
      i. Must have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
      ii. If hormone receptor (HR)-positive disease, must have tried and failed, intolerance, or contraindication at least one line of endocrine therapy
      iii. HER2-low breast cancer is defined as follows:
         1. IHC is 1+
         OR

2. IHC 2+ with a negative ISH result defined by any of the following:
    a) Dual probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number less than 4.0 signals/cell
    b) Dual probe HER2/CEP17 ratio greater than or equal to 2.0 with an average HER2 copy number less than 4.0 signals/cell
    c) Dual probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 4.0 signals/cell and less than 6.0 signals/cell

iv. Must never have had breast cancer diagnosed as HER2-positive
v. Must not have been previously treated with any anti-HER2 therapy

e. Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations
    i. Must have been previously treated with at least one prior systemic therapy
f. Locally advanced, recurrent, or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma
    i. Must be used as subsequent therapy
    ii. HER2 positive is defined as follows:
        1. Immunohistochemistry (IHC) is 3+
        OR
        2. In situ hybridization (ISH) positive by any of the following:
            a) Single probe average HER2 copy number greater than or equal to 6.0 signals/cell
            OR
            b) Dual probe HER2/CEP17 ratio greater than or equal to 2.0
            OR
            c) Dual probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell
g. Unresectable or metastatic HER2-positive solid tumors
    i. HER2 positive is defined as immunohistochemistry (IHC) 3+
    ii. Must have received prior systemic treatment and have no satisfactory alternative treatment options
h. Must not have a left ventricular ejection fraction of less than 50% prior to starting therapy
i. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
    a. Quantity Limits: Align with FDA recommended dosing
    b. Authorization Period: Aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days and up to 6 months at a time
    c. Renewal Criteria: Continuation of therapy until disease progression or unacceptable toxicity

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Enhertu is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for:
    - Adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
    - Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
    - Adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
    - The treatment of adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.
    - Adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options
- Per the 2024 NCCN guidelines for breast cancer, define HER2-positive breast cancer as:
    - Tumors with an IHC of 3+, OR
    - ISH positive by any of the following:
        - Single probe average HER2 copy number greater than or equal to 6.0 signals/cell, OR
        - Dual probe HER2/CEP17 ratio greater than or equal to 2.0, OR
        - Dual probe HER2/CEP17 ratio less than 2.0 with an average HER2 copy number greater than or equal to 6.0 signals/cell
- Safety and efficacy for use in metastatic HER2-positive breast cancer previously treated with two or more anti-HER2 therapies were evaluated in the phase II DESTINY-Breast01 trial, an open-label, single-arm study involved 184 women. All patients had been previously treated with Kadcyla. Patients were excluded from the study if they had a history of noninfectious interstitial lung disease or pneumonitis resulting in the use of glucocorticoids or current or suspected interstitial lung disease or pneumonitis. Patients were also excluded if they had a left ventricular ejection fraction less than 50%. The primary endpoint was the confirmed objective response rate (ORR). A response to therapy was reported in 112 patients (60.9%; 95% confidence interval [CI]: 53.4 to 68.0). The median duration of follow-up was 11.1 months (range 0.7 to 19.9). The median response duration was 14.8 months (95% CI: 13.8 to 16.9), and the median duration of progression-free survival was 16.4 months (95% CI: 12.7 to not reached).
- The 2024 National Comprehensive Cancer Network (NCCN) breast cancer treatment guidelines recommend Enhertu as second-line therapy for unresectable or metastatic breast cancer and for use as first-line therapy in situations where there has been rapid progression within 6 months following adjuvant or neoadjuvant therapy or within 12 months for those on a pertuzumab-containing regimen. The addition to the guidelines was based on the DESTINY-Breast03 trial, a randomized phase 3 study comparing safety and efficacy of Enhertu to Kadcyla® in 524 patients with HER2+ metastatic breast cancer who were previously treated with trastuzumab and a taxane. The primary endpoint

was progression-free survival (PFS). The hazard ratio in progression-free survival was 0.28. Overall survival had a hazard ratio of 0.56 and p-value = 0.007. The 12-month overall survival rate was 94% with Enhertu versus 86% for Kadcyla. There was an objective response rate in 80% of patients receiving Enhertu and 34% on Kadcyla. Only 1.1% of patients had progressive disease as best response.

- Safety and efficacy for use in unresectable or metastatic HER2-low breast cancer were evaluated in the phase III DESTINY-Breast04 trial, a randomized, two-group, open-label trial study of 557 adult patients with unresectable or metastatic HER2-low breast cancer. The study included 2 cohorts: 494 hormone receptor-positive (HR+) patients and 63 hormone receptor-negative (HR-) patients. HER2-low expression was defined as IHC 1+ or IHC 2+ with a negative ISH. Patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Patients who were HR+ must have received at least one endocrine therapy or be ineligible for endocrine therapy. Treatment was administered until disease progression, death, withdrawal of consent, or unacceptable toxicity. The study excluded patients with a history of interstitial lung disease (ILD) or pneumonitis requiring treatment with steroids or ILD/pneumonitis at screening and clinically significant cardiac disease. The primary endpoint was PFS. Among all patients, the median PFS was 9.9 months (95% CI: 9.0, 11.3) in the Enhertu group and 5.1 months (95% CI: 4.2, 6.8) in the physician's choice group (hazard ratio for disease progression or death 0.50; 95% CI: 0.40, 0.63; p-value <0.001). A consistent benefit was observed for Enhertu across all analyzed subgroups.

- Safety and efficacy for use in unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations were evaluated in the DESTINY-Lung02 trial, a multicenter, multi-cohort, randomized, blinded, dose-optimization study of 52 patients with unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after one prior systemic therapy. Patients with a history of steroid dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status greater than 1 were excluded. Patients received Enhertu 5.4 mg/kg by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was confirmed ORR. An interim efficacy analysis in a pre-specified patient cohort showed Enhertu demonstrated a confirmed ORR of 57.7% (95% CI: 43.2, 71.3). Complete responses (CR) were seen in 1.9% of patients and partial responses (PR) in 55.8% of patients with a median DoR of 8.7 months (95% CI: 7.1 - NE).

- Safety and efficacy for use in metastatic locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma were evaluated in the phase II DESTINY-Gastric01 trial, a randomized, open-label study of a total of 188 patients who had progressed on at least two prior regimens, including trastuzumab. Patients were excluded from the study if they had a history of noninfectious interstitial lung disease or pneumonitis resulting in the use of glucocorticoids or current or suspected interstitial lung disease or pneumonitis. Patients were also excluded if they had a left ventricular ejection fraction less than 50%. The primary endpoint was the confirmed ORR. Patients treated with Enhertu had a longer median overall survival (12.5 months vs. 8.4 months) and a higher confirmed overall response rate (40.5% vs. 11.3%) compared with the other arms. Results for progression-free survival (median, 5.6 months vs. 3.5 months) and duration of response (median, 11.3 months vs. 3.9 months) also favored the Enhertu group.

- Safety and efficacy for use in metastatic HER2-positive solid tumors were established in three clinical trials of 192 total patients with previously treated unresectable/metastatic HER2-positive (IHC3+) solid tumors: DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02. DESTINY-PanTumor02 involved patients with different types of solid tumors, whereas DESTINY-Lung01 enrolled patients with lung cancer and DESTINY-CRC02 patients with colorectal cancer. Patients must have been previously treated and have no other satisfactory treatment options available prior to Enhertu use. All three studies excluded patients if they had a history of noninfectious interstitial lung disease or pneumonitis resulting in the use of glucocorticoids or current or suspected interstitial lung disease or pneumonitis. The primary endpoint was the objective response rate (ORR). Median duration of response (DOR) also was evaluated. DESTINY-PanTumor02 subjects has an ORR of 51.4% and DOR of 19.4 months. There was a

52.9% ORR and 6.9 month DOR for DESTINY-Lung02. DESTINY-CRC02 has an ORR of 46.9% and DOR of 5.5 months.

References:

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Policy History		
#	Date	Change Description
2.0	Effective Date: 06/06/2024	Updated to include the new indication for use in unresectable or metastatic HER2-positive (IHC 3+) solid tumors
1.9	Effective Date: 04/11/2024	Updated to include recurrent HER2-positive gastric or gastroesophageal junction adenocarcinoma, require Enhertu is used as subsequent therapy, and to remove the requirement that the patient does not have interstitial lung disease or pneumonitis
1.8	Effective Date: 04/06/2023	Updated approval length to allow authorization for at least 60 days
1.7	Effective Date: 10/06/2022	Updated to include the new indications for use in HER2 low breast cancer and NSCLC
1.6	Effective Date: 04/14/2022	Updated to allow use as second-line therapy in unresectable or metastatic breast cancer or as first- line therapy in patients with rapid progression following adjuvant or neoadjuvant therapy for breast cancer which is allowed per the NCCN guidelines andto update approval length to allow for FDA recommended dosing or up to 6 months at a time
1.5	Effective Date: 04/08/2021	Updated to include the new indication of locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma

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<tr><td>1.4</td><td>Effective Date: 02/04/2021</td><td>Annual review of criteria was performed, no changes were made.</td></tr>
<tr><td>1.3</td><td>Effective Date: 12/01/2020</td><td>UM medical management system update for BCBS
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.2</td><td>Effective Date: 04/01/2020</td><td>UM medical management system update for MAPPO and BCNA
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<tr><td>1.0</td><td>Effective Date: 02/06/2020</td><td>New full drug review</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*